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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,637	12/30/2003	Nancy L. Brackett	7230-9	6890

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EXAMINER

SCHUBERG, LAURA J

ART UNIT PAPER NUMBER

1657

DATE MAILED: 11/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/748,637	Applicant(s) BRACKETT ET AL.	
	Examiner Laura Schuberg	Art Unit 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear from claim 7 if the biological sample includes only fluid from the female reproductive tract or comprises both sperm and fluid from the female reproductive tract. For examination purposes the biological sample is interpreted to comprise both. Inserting the phrase, "wherein the biological sample further comprises" into claim 7 would improve clarity in this case.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 6, 8-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

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Claim 1 is drawn to a method of increasing motility of sperm by providing from a subject a biological sample comprising sperm and at least one cytokine and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

Claim 2 includes wherein the subject has a condition that impairs fertility.

Claim 5 includes wherein the sample comprises fluid from the male reproductive tract.

Claim 6 includes wherein the sample comprises semen.

Claims 8-15 include wherein the agent is an antibody that specifically binds to the at least one cytokine.

Alexander teaches the use of sandwich ELISA for cytokines in a semen sample (column 11 line 5). The use of antibodies that specifically bind to the cytokines in the semen such as TNF α , IL1 β , and IL6 is taught (column 11 line 10) (claims 1, 5, 6, 8-15). The subject's condition causes increased cytokine levels in the semen, which inherently impairs fertility (as taught by Applicant page 5 lines 1-5).

Since Alexander is explicitly practicing all the steps of Applicant's method as claimed by administering cytokine antibodies that specifically bind to the claimed cytokines in a semen sample, Alexander anticipates Applicant's claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148

USPQ 459 (1966), that are applied for establishing a background for determining

obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1) in view of Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999).

Claims 1, 2, 5, 6 and 8-15 are drawn to the method as described above.

Claims 16-19 include wherein the agent is a soluble cytokine receptor that specifically binds to the at least one cytokine, TNF α , IL1 β , and IL6.

Alexander teaches a method that provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen comprising administering one or more ant-cytokine agents (column 7 line 35). Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8). The use of antibodies that specifically bind to the cytokines such as TNF α , IL1 β , and IL6 is taught (column 11 line 10) as well

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as the use of soluble cytokine receptors that bind to the cytokines TNF α , IL1 β , and IL6 (column 29, US 5,770,401). Alexander also teaches that various modifications would become apparent to those of skill in the art upon review of reference's disclosure (column 51 lines 8-13).

Alexander does not specifically teach treating infertility by contacting a semen sample that contains cytokines with an agent that inactivates or reduces the activity of the cytokines.

Gruschwitz teaches that patients exhibiting increased levels of TNF α , IL1 β , and IL6 showed a significantly reduced amount of progressively motile spermatozoa (page 162 column 2 lines 17-20). These cytokines may result in decreased sperm motility and therefore in reduced ova-penetrating properties (page 162 column 2 lines 42-47).

Angelopoulos teaches a method for enhancing sperm motility that is an alternative to applying motility stimulants for intracytoplasmic sperm injection (page 240). Angelopoulos also teaches the advantages and disadvantages of the different methods of enhancing sperm motility of a semen specimen (page 243, column 1, 2nd paragraph).

One of ordinary skill in the art would have been motivated to use the method of Alexander as a treatment for infertile males because Gruschwitz teaches a connection between patients with increased levels of TNF α , IL1 β , and IL6 and reduced sperm motility (page 162 column 2 lines 17-20) and because the method of Alexander provides for treating men determined to be suffering from a disorder associated with elevated levels of one or more cytokines in one or more components or fractions of semen

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comprising administering one or more ant-cytokine agents (column 7 line 35). One of ordinary skill in the art would have been motivated to use the method of Alexander directly on semen samples, such as in intracytoplasmic sperm injection (ICSI-which is a treatment for male infertility) because Angelopoulos teaches that ICSI benefits from enhancement of sperm motility and that there are several alternatives for accomplishing this (page 240). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as ICSI). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches that compounds that interfere with the production and/or activity of various cytokines are widely known and that such compounds may bind to the cytokine or its receptor, thereby preventing the natural cytokine-receptor interaction (column 7-8).

Therefore, the combined teachings of Alexander, Gruschwitz and Angelopoulos render obvious Applicant's invention as claimed.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Basu et al (Journal of Andrology 2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art

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only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 1, 2, 5, 6, 8-19 are drawn to the method as described above.

Claim 3 is drawn to the method of claim 2 wherein the condition that impairs fertility is leukocytospermia.

Claim 4 is drawn to the method of claim 1 wherein the subject has SCI (spinal cord injury).

The combined teachings of Alexander Gruschwitz and Angelopoulos provide the method of claims 1, 2, 5, 6, 8-19 as described above, but do not teach wherein the subject has leukocytospermia or an SCI. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine,

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such as TNF α (column 5 line 12) and that there is a connection between leukospermia and levels of IL-6 (references cited, Shimoya et al).

Basu teaches that there is a relationship between leukocytospermia and decreased sperm motility in the semen of men with SCI (abstract). Basu also teaches that it is reasonable to assume that most of the abnormal levels of cytokines in the semen can be attributed to the abnormal levels of cytokine-producing cells (leukocytes) found in these patients and that they have a detrimental effect on sperm motility (p.555).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat men with SCI and leukocytospermia because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine (column 5 line 12) and Basu teaches that men with SCI and leukocytospermia have elevated levels of cytokines (p.555). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that require collection of the semen sample prior to fertilization (such as with spinal cord injured patients). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches the use of anti-cytokine compounds for IL-6 and also that there is a connection between IL-6 and leukospermia (also known as leukocytospermia).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos and Basu render obvious Applicant's invention as claimed.

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Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Brackett et al (Physical Therapy 1996):

Claims 1- 6, 8-19 are drawn to the method as described above.

The combined teachings of Alexander, Gruschwitz and Angelopoulos provide the method of claims 1, 2, 5, 6, 8-19 as described above, but do not teach wherein the subject has leukocytospermia or an SCI. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine, such as TNF α (column 5 line 12) and that there is a connection between leukospermia and levels of IL-6 (references cited, Shimoya et al).

Brackett teaches that leukocytospermia is observed in many men with SCI and that this condition is thought to contribute to poor semen quality because studies indicate an association with reductions in sperm motility and loss of sperm function as a result of cytotoxic cytokines (page 1227 column 1, 2nd paragraph).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat men with SCI and leukocytospermia because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine (column 5 line 12) and Brackett teaches that men with SCI and leukocytospermia have cytotoxic levels of cytokines (p.1227). In addition, treatment of a sperm sample would be an obvious alternative to directly injecting the agent into the patient (such as taught by Alexander) where fertilization was to be accomplished by alternative methods that

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require collection of the semen sample prior to fertilization (such as with spinal cord injured patients). One of ordinary skill in the art would have had a reasonable expectation of success because Alexander teaches the use of anti-cytokine compounds for IL-6 and also that there is a connection between IL-6 and leukospermia (also known as leukocytospermia).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos and Brackett render obvious Applicant's invention as claimed.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Gerris (European Society of Human Reproduction and Embryology 1999).

Claims 1, 2, 5, 6 and 8-19 are drawn to the method as described above.

Claim 7 is drawn to the method of claim 1 wherein the biological sample comprises a fluid produced by the female reproductive tract.

The combined teachings of Alexander Gruschwitz and Angelopoulos provide the method of claims 1, 2, 5, 6, 8-19 as described above, but does not include wherein the biological sample comprises a fluid produced by the female reproductive tract. However, Alexander does teach that the method may be used to treat conditions associated with elevated levels of a cytokine, such as TNF α (column 5 line 12). Angelopoulos teaches

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that there are several different methods for treating sperm motility of specimen as described above.

Gerris teaches that although the standard method for collection of a sperm sample is by masturbation, other approaches have been described and assessed. The use of spermatozoa obtained from the vagina or the cervix after full coitus has been suggested for use in ICSI in patients who wish to avoid masturbation for religious reasons and has been described as an excellent alternative to masturbation (page 213 column 2).

One of ordinary skill in the art would have been motivated to use the method of Alexander to treat semen samples obtained from a woman's reproductive tract because Gerris teaches that this is an excellent alternative for sperm collection for patients who are opposed to masturbation for religious reasons. One of ordinary skill in the art would have had a reasonable expectation of success because this collection method had been used previously for infertility with success (page 213 column 2).

Therefore, the combined teachings of Alexander, Gruschwitz, Angelopoulos, and Gerris render obvious Applicant's invention as claimed.

Response to Arguments

Applicant's arguments and declarations filed 09/13/2006 have been fully considered but they are not persuasive. The arguments and declarations have been addressed as far as they pertain to the new rejections above.

Applicant argues that the Alexander reference does not teach methods of increasing sperm motility. Applicant argues that treatment of sexual dysfunction by administering anti-TNF α antibodies with a patient suffering from CPPS has no bearing on treating fertility. Applicant argues that Alexander neither teaches nor discloses treatment of actual semen samples with any anti-cytokine agents.

This is not found persuasive because the Alexander reference is not limited to its preferred embodiments. Alexander does suggest that the method can be used to treat conditions associated with elevated levels of a cytokine (column 5 line 12) and this would motivate one of ordinary skill in the art to look to other disorders that have been linked to elevated cytokine levels (such as male infertility and leukocytospermia). In addition, Alexander does obtain a semen specimen and contacts it with antibodies that bind to cytokines in the ELISA method. Since Alexander is explicitly practicing all the steps of Applicant's method as claimed by administering cytokine antibodies that specifically bind to the claimed cytokines in a semen sample, Alexander anticipates Applicant's claimed method.

Applicant argues that there is no motivation to combine Alexander and Basu, as each discuss different conditions and diagnosis of CPPS as discussed by Alexander would not result in a method of treatment for infertility as taught by the instant invention.

This is not found persuasive since both references deal with elevated levels of cytokines in the semen. In addition, Alexander does teach a method that is not limited to CPPS, but includes conditions associated with elevated cytokines as well. Alexander also teaches that various modifications would become apparent to those of skill in the

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art upon review of reference's disclosure (column 51 lines 8-13). This would provide motivation for one of ordinary skill in the art to modify the method of Alexander to address other conditions with regard to cytokine levels in the semen.

Applicant argues that Basu is not a proper reference because Basu is a co-inventor of the present Application. This is not found persuasive because the Basu reference includes authors that are not co-inventors of the present Application and thus is a proper prior art reference since it originates from a different inventive entity than the Application does. Directions for overcoming this rejection are provided above.

Conclusion

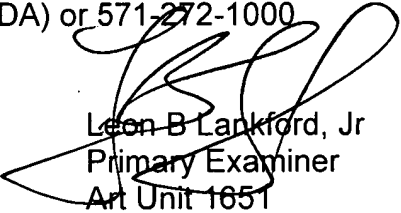
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura Schuberg whose telephone number is 571-272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Leon B Lankford, Jr
Primary Examiner
Art Unit 1651

Laura Schuberg